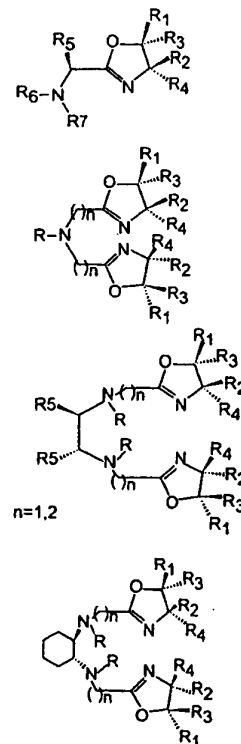




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(21) International Application Number: PCT/US98/24036 (22) International Filing Date: 12 November 1998 (12.11.98) (30) Priority Data: 60/065,502 12 November 1997 (12.11.97) US (71) Applicant: THE PENNSYLVANIA STATE UNIVERSITY [US/US]; 113 Technology Center, 200 Innovation Boulevard, University Park, PA 16802-7000 (US). (72) Inventor: ZHANG, Xumu; Department of Chemistry, The Pennsylvania State University, 152 Davey Laboratory, Uni- versity Park, PA 16802 (US). (74) Agents: GARRETT, Arthur, S. et al.; Finnegan, Henderson, Farabow, Garrett & Dunner, L.L.P., 1300 I Street, N.W., Washington, DC 20005-3315 (US).		(81) Designated States: AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, CA, CH, CN, CU, CZ, DE, DK, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MD, MG, MK, MN, MW, MX, NO, NZ, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TR, TT, UA, UG, UZ, VN, YU, ZW, ARIPO patent (GH, GM, KE, LS, MW, SD, SZ, UG, ZW), Eurasian patent (AM, AZ, BY, KG, KZ, MD, RU, TJ, TM), European patent (AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE), OAPI patent (BF, BJ, CF, CG, CI, CM, GA, GN, GW, ML, MR, NE, SN, TD, TG). Published <i>With international search report.</i> <i>Before the expiration of the time limit for amending the</i> <i>claims and to be republished in the event of the receipt of</i> <i>amendments.</i>
(54) Title: TRANSITION METAL-CATALYZED REACTIONS BASED ON CHIRAL AMINE OXAZOLINYL LIGANDS (57) Abstract The invention is drawn to novel transition metal catalysts for the practical synthesis of important chiral molecules. The transition metal catalysts comprise chiral ligands based on chiral amine oxazolinyl ligands. The invention includes methods of making the catalysts, and methods of performing reactions using the catalysts.		



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**TRANSITION METAL-CATALYZED REACTIONS
BASED ON CHIRAL AMINE OXAZOLINYL LIGANDS
CROSS REFERENCE TO RELATED APPLICATIONS**

This application claims priority to U.S. provisional application 60/065,502, filed November 12, 1997, incorporated by reference in its entirety.

BACKGROUND OF THE INVENTION

Molecular chirality plays an important role in science and technology. The biological activities of many pharmaceuticals, fragrances, food additives and agrochemicals are often associated with their absolute molecular configuration. While one enantiomer gives a desired biological function through interactions with natural binding sites, another enantiomer usually does not have the same function and sometimes has deleterious side effects. A growing demand in pharmaceutical industries is to make chiral drugs in enantiomerically pure form. To meet this fascinating challenge, chemists have explored many approaches for acquiring enantiomerically pure compounds ranging from optical resolution and structural modification of naturally occurring chiral substances to asymmetric catalysis using synthetic chiral catalysts and enzymes. Among these methods, asymmetric catalysis is perhaps the most efficient because a small amount of a chiral catalyst can be used to produce a large quantity of a chiral target molecule. During the last several decades, great attention has been devoted to discovering new asymmetric catalysts and more than a half-dozen commercial industrial processes have used asymmetric catalysis as the key step in the production of enantiomerically pure compounds. The worldwide sales of chiral drugs in 1997 was nearly \$90 billion.

Many chiral phosphines have been made to facilitate asymmetric reactions. Among these ligands, BINAP is one of the most frequently used bidentate chiral phosphines. The axially dissymmetric, fully aromatic BINAP ligand has been demonstrated to be highly effective for many asymmetric

reactions. DUPHOS and related ligands have also shown impressive enantioselectivities in numerous reactions. However, these phosphines are difficult to make and some of them are air sensitive. Recently, chiral nitrogen ligands have been extensively studied for asymmetric reactions. Particularly, oxazolinyls derived from chiral amino alcohols are popular ligands. Recognition of secondary interaction between ligands and substrates have also been used to design asymmetric catalysts. For example, primary and secondary amines may form H-bonds with substrates.

SUMMARY OF THE INVENTION

An object of the present invention is the development of novel transition metal complexes with new families of amine oxazolinyl ligands for practical asymmetric synthesis. Several new families of chiral amine oxazolinyl ligands for asymmetric catalysis are embodied herein, including secondary amine oxazolinyl ligands, and amine oxazolinyl ligands having more than one oxazolinyl group.

A further object of the invention is the preparation of the chiral oxazolinyl from chiral amino alcohols.

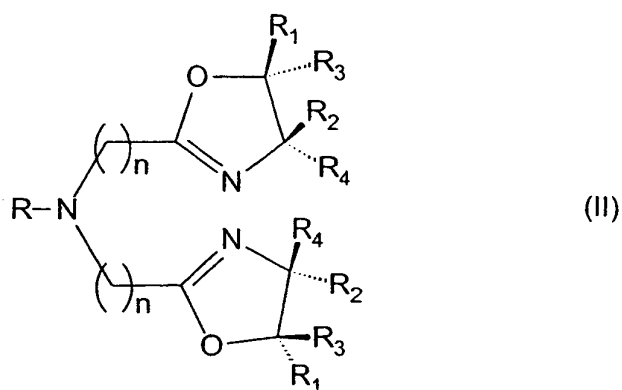
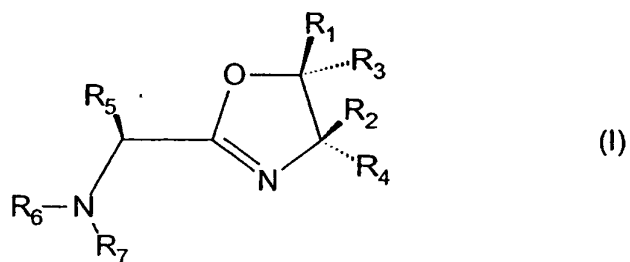
A further object of the invention is the discovery of chiral tridentate and tetradentate ligands suitable for asymmetric catalysis. Particularly, these ligands have been demonstrated to be highly effective for Ru-catalyzed transfer hydrogenation of ketones and imines.

A further object of the invention is the improved catalysis of transition metal facilitated reactions such as hydrogenation, hydride transfer reaction, hydrosilylation, hydroboration, hydrovinylation, hydroformylation, hydrocarboxylation, allylic alkylation, cyclopropanation, Diels-Alder reaction, Aldol reaction, Heck reaction, Michael addition, and rearrangement reactions, leading to efficient and practical methods for producing important chiral drugs and agrochemicals.

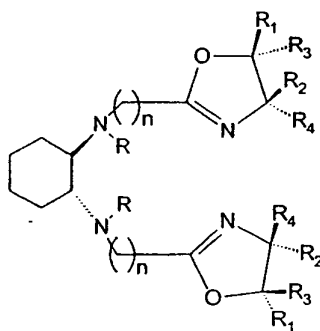
To achieve the objects and in accordance with the purpose of the invention as embodied and broadly described herein, the invention comprises

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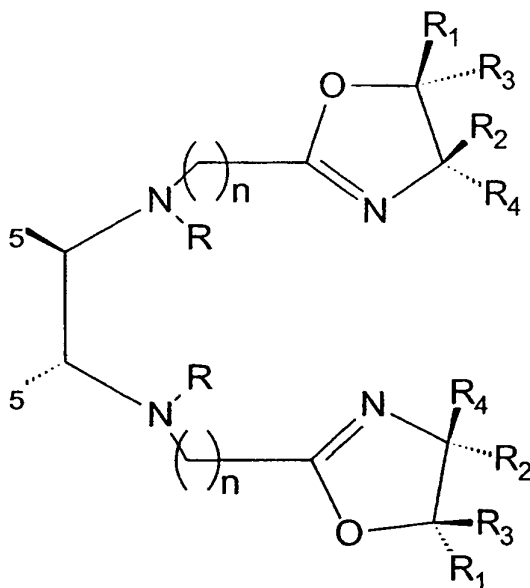
a chiral ligand that forms a catalyst providing enhanced enantiomeric selectivity in asymmetric reactions, having a structure selected from the group consisting of the enantiomers of the following formulas (I) through (IV):



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(IV)



(III)

wherein R_1 , R_2 , R_3 , R_4 , R_5 , R_6 and R_7 are independently hydrogen, alkyl, aryl, substituted alkyl or substituted aryl, wherein any two of R_1 , R_2 , R_3 and R_4 , may be linked to each other to form ring structures, wherein any two of R_5 , R_6 and R_7 may be linked to each other to form a ring structure, and wherein n is 1 or 2.

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BRIEF DESCRIPTION OF FIGURES

Figure 1 shows a general synthesis route for a bis(oxazolinylmethyl)amine (hereinafter "AMBOX") ligand in a preferred embodiment of the present invention.

Figure 2 shows the general structure of several chiral ligands according to preferred embodiments of the present invention.

Figure 3 shows specific examples of the chiral ligands according to preferred embodiments of the present invention.

Figure 4 is a schematic depiction of transition metal catalysts of chiral tridentate nitrogen ligands with an NH function, showing the cyclic transition state obtained in the transfer hydrogenation of prochiral ketones.

DETAILED DESCRIPTION OF THE PREFERRED EMBODIMENTS

Asymmetric catalytic transfer hydrogenation using 2-propanol as a hydrogen source offers an attractive route for reducing unsymmetric ketones to chiral alcohols. Among the recently developed efficient transition-metal-based chiral catalysts, the most notable is the Ru(II)-TsDPEN (N-(*p*-tolylsulfonyl)-1,2-diphenylethylene-diamine) system reported by R. Noyori, et al., "Asymmetric Transfer Hydrogenation Catalyzed by Chiral Ruthenium Complexes," *Acc. Chem. Res.*, Vol. 30, No. 2, pp. 97-102 (1997) and K. Haack, et al., "The Catalyst Precursor, Catalyst and Intermediate in the Ru"-promoted Asymmetric Hydrogen Transfer Between Alcohols and Ketones," *Angew. Chem. Int. Engl.*, Vol. 36, No. 3 pp. 285-288 (1997), which are incorporated herein in their entirety. They suggest that an NH moiety in the ligand may promote a cyclic transition state through hydrogen bonding to a ketone substrate, greatly increasing substrate affinity to the catalyst active site, inducing high activity and optical purity. Other reports have shown a similar "NH effect", for example, J. Gao, et al. "A Ruthenium(II) Complex with a C₂ symmetric Diphosphine/Diamine Tetradentate Ligand for Asymmetric Transfer Hydrogenation of Aromatic Ketones," *Organometallics*, Vol. 15, No. 4, pp. 1087-1089 (1996) and P. Gamez, et al., "Asymmetric Catalytic

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Reduction of Carbonyl Compounds Using C₂ symmetric Diamines as Chiral Ligands," *Tetrahedron: Asymmetry*, Vol. 6, No. 3, pp. 705-718 (1995), which are incorporated herein in their entirety.

In an effort to develop chiral tridentate ligands for asymmetric catalysis, we have designed the bis(oxazolinylmethyl)amine ("AMBOX") ligand system. Chiral tridentate ligands tend to form a deep chiral pocket around the metal center once coordinated to a transition metal. A good example is the well known PYBOX ligand family, disclosed, for example by H. Nishiyama, "Chiral and C₂-Symmetrical Bis(oxazolinylpyridine)rhodium(III) Complexes: Effective Catalysts for Asymmetric Hydrosilylation of Ketones," *Organometallics*, Vol. 8, No. 3, pp. 846-48 (March 1989). This catalyst has been successfully applied to the catalysis of asymmetric reactions. The two R groups on the oxazoline rings of PYBOX form a highly enantioselective "chiral fence," which enables better differentiation of the *Re* and *Si* faces of incoming substrates.

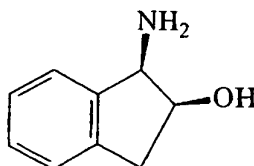
By replacing the pyridine backbone of PYBOX with an amine function, the new ligand AMBOX undergoes cyclic transition states similar to those suggested in the Noyori and Haack articles cited above and effectively catalyzes asymmetric transformations—for instance, the hydride-transfer reduction of ketones. **Figure 4** is a schematic depiction of the cyclic transition state obtained in the transfer hydrogenation of prochiral ketones.

Figure 1 depicts a preferred synthetic route for bis[4-(R)-phenyloxazolin-2-yl-methyl]amine (hereinafter "(R)-Ph-AMBOX"), a preferred embodiment of the present invention. A cyanoamine is reacted at **a** with HCl and methyl alcohol to form an imidate ester hydrochloride in 76% crude yield. The obtained imidate hydrochloride is reacted at **b** without further purification with an (R)-phenyl glycinol in dichloromethane at between 0°C and room temperature for twelve hours. (R)-Ph-AMBOX was obtained in 15% yield.

The chirality of the oxazolinyl amine product as well as the identity of the substituents may be determined by choosing a different amino alcohol for

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step b. For example, to form preferred structure XI shown in Figure 3, the amino alcohol



may be used in step b. In the scheme set forth in Fig. 1, the (S) amino alcohol may be used to achieve a product with opposite chirality.

The catalysts of the present invention are produced by complexing the herein described amine-oxazolinyl ligands with a transition metal. Suitable transition metal catalyst precursors for complexing with the chiral ligand of the present invention are known to those of ordinary skill in the art. For example, $[\text{Rh}(\text{cod})\text{Cl}]_2$, $[\text{Rh}(\text{cod})_2]\text{X}$, $[\text{Ir}(\text{cod})\text{Cl}]_2$, $[\text{Ir}(\text{cod})_2]\text{X}$, $\text{Ru}(\text{cod})\text{Cl}_2$, where "cod" means 1,5-cyclooctadiene, and X stands for BF_4 , ClO_4 , SbF_6 , CF_3SO_3 , or equivalents, may be used. Alternatively, $\text{RuCl}_2(\text{PPh}_3)_3$, $\text{RuHCl}(\text{PPh}_3)_3$, $\text{RuX}_2(\text{PR}_3)_3$, $\text{RuHX}(\text{PR}_3)_3$, RuX_2 , and other equivalents may be used, wherein X is halogen and R is a substituted or unsubstituted alkyl or aryl group.

Optimization of Catalyst

Initial test results on transfer hydrogenation of acetophenone in 2-propanol, using catalysts made *in situ* with AMBOX and various commonly used transition metal precursors were disappointing. Poor enantioselective performance prevailed among all these catalysts, with the highest enantiomeric excess (alternatively referred to as "ee" herein) of less than 50% obtained using $\text{RuCl}_2(\text{PPh}_3)_3$.

Table 1 presents the results of optimization of catalytic conditions for the transfer hydrogenation of acetophenone using (R)-Ph-AMBOX. Reaction (1) below was carried out in a 0.1 M acetophenone solution in 5mL 2-propanol. The ratio of ketone : Ru^{II} : (R)-Ph-AMBOX was 100:1:1.1.

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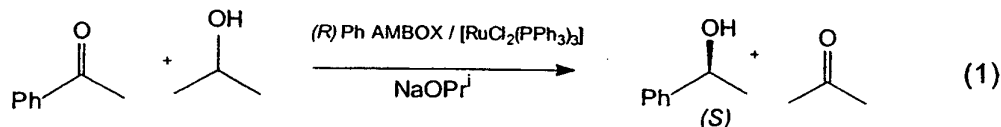


TABLE 1

Entry	Free PPh ₃ ^a	NaOPr ⁱ equiv. ^b	T °C	t h	yield ^c %	ee ^c %
1 ^d	+	15	82	0.5	96	45
2 ^e	+	15	82	.025	92	60
3	+	1.0	82	1	67	84
4	-	1.0	82	0.17	91	97
5	-	0.5	82	1	26	95
6	-	0	82	1	0	N/A
7	-	2.0	82	0.17	94	68
8	-	1.0	23	22	91	95

a. "+" indicates free PPh₃ existed in the reaction mixture; "-" indicates that free PPh₃ was washed out with ether after the catalyst was formed, before adding acetophenone and NaOPrⁱ

b. Equivalents of base to Ru^{II}

c. % Yield and % enantiomeric excess were determined by GC analysis with a chiral Supelco β-DEX 120 capillary column. Absolute configurations were determined by comparing optical rotations with literature values. All major secondary alcohol products are (S) isomers.

d. Catalyst made by stirring a mixture of R-(Ph)-AMBOX and RuCl₂(PPh₃)₃ at room temperature overnight.

e. For entries 2-8, catalysts were prepared by refluxing R-(Ph)-AMBOX and RuCl₂(PPh₃)₃ at 82°C for two hours.

It was found that an *in situ* catalyst made by refluxing AMBOX and RuCl₂(PPh₃)₃ in 2-propanol was far more effective than a catalyst made at room temperature. For entries 2 and 8 on Table 1, the catalysts were

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prepared by refluxing the $\text{RuCl}_2(\text{PPh}_3)_3$ precursor at 82°C for two hours. These catalysts produced greater enantiomeric excess than the corresponding catalysts of entry 1, which were prepared overnight at room temperature. Thus, according to a preferred embodiment of the present invention, the catalysts are prepared by refluxing at the boiling temperature of 2-propanol.

Another factor that can drastically enhance both catalytic activity and enantioselectivity is the removal of free triphenylphosphine ligand released during the complexation of AMBOX before introducing acetophenone and base (NaOPr^i). Free PPh_3 may interfere with the reaction due to its ability to complex with the Ru center again. Removal of free PPh_3 reduces unfavorable competition to the enantioselective catalytic process. Preferably according to the invention, a mixture of $\text{RuCl}_2(\text{PPh}_3)_3$ precursor is heated with R-Ph-AMBOX for two hours, yielding a green solution. After the solvent is removed on vacuum, the resulting greenish residue is washed with ether to remove any free PPh_3 . The solid is redissolved in 2-propanol, followed by addition of substrate and NaOPr^i . The enantiomeric excess increased dramatically from 84% to 97% upon such treatment, as may be seen by comparing entries 3 and 4 of Table 1.

Another important factor that can enhance activity and enantioselectivity is the molar ratio of NaOPr^i to catalyst. This ratio should be about 1.0. When 0.5 molar equivalent of base was used, the reaction became very sluggish, although the enantiomeric excess remained high (entry 5, Table 1). When 2.0 molar equivalents of base were used, the reaction accelerated, but accompanied by severe erosion of enantiomeric excess (entry 7, Table 1).

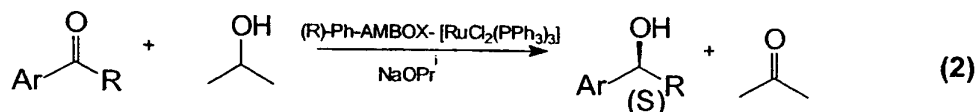
Figure 4 depicts the presumed active catalyst species conformation, wherein L represents PPh_3 and X represents chlorine. The species of Figure 4 is probably formed after one HCl is extracted by one NaOPr^i from the supposed precursor of $\text{RuCl}_2\text{PPh}_3(\text{AMBOX})$, followed by abstraction of one

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proton and one hydride from 2-propanol. The chloride across from the apical PPh_3 should be preferentially removed together with the NH proton, considering a strong trans effect from PPh_3 . However, if more than one molar equivalent of base is introduced, the chloride across from NH could also be removed, resulting in possible pathways that favor the reverse reaction of ketone reduction, and hence a rapid loss of enantiomeric excess. Free PPh_3 may also interfere with the reaction, due to its ability to complex with the ruthenium center again. Therefore, removal of free PPh_3 should see unfavorable competition to the enantioselective catalytic process diminished. Indeed, enantiomeric excess dramatically increased from 84% to 97% upon such treatment. (See entries 3-4 in Table 1).

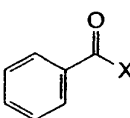
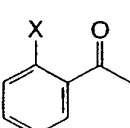

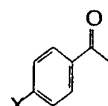
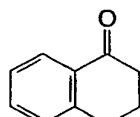
Table 2 depicts the reduction of a variety of aromatic ketones to their secondary alcohols under optimized conditions using the catalyst of the present invention, with high enantiomeric excess and mostly satisfactory yield. The generic reaction (2) was carried out (except as otherwise stated) using a 0.1 M ketone solution in 5 mL 2-propanol. The ratio of ketone:Ru:(R)-Ph-Ambox:NaOPr was 100:1:1.1:1.0.



Various changes in substrates and catalytic reaction conditions are shown in Table 2 below.

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TABLE 2

Entry	Ketone	t min	yield ^a %	ee ^a %	
1		X = CH ₃	5 (10)	80 (91)	98 (97)
2		X = Et	10 (20)	77 (92)	95 (92)
3		X = i-Pr	10	15	78
4		X = CH ₃	40	96	98
5		X = Cl	10	99	96
6		X = CH ₃ O	4h	3	19
7		X = CH ₃	5 (7)	75 (90)	96 (94)
8		X = Cl	10	5	92
9		X = CH ₃ O	7 (10)	91 (94)	95 (93)
10		X = CH ₃	24h/rt	61	96
11		X = Cl	10	97	90
12		X = CH ₃ O	10	41	98
13			10	42	95

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substituted at the two position with an alkyl amine or substituted alkyl amine. As seen in Formula (I) for example, the alkyl amine substituted at the 2 position of the oxazole may be, for example, a methylamine or a substituted methylamine. Moreover, the amine may be a primary, secondary or tertiary amine as shown in Figure 2.

In **Figure 2**, R_1 , R_2 , R_3 , R_4 , R_5 , R_6 and R_7 may be the same or different and may be hydrogen, alkyl, aryl, substituted alkyl, or substituted aryl. Also within the scope of the invention are embodiments wherein any two of R_1 , R_2 , R_3 and R_4 may be linked to form a ring structure, and wherein any two of R_5 , R_6 and R_7 may be linked to form a ring structure. For example, in Formula (II), where R_1 and R_3 are methyl and R_2 and R_4 are phenyl, a structure having the configuration of Formula (XI) is formed. Likewise, one of ordinary skill in the art would recognize many ring structures made possible by joining R_1 through R_4 in Formulas (I) through (IV). Alternatively, a ring formed by linking R_5 and R_6 could form a structure like that shown in Formula (VI).

Although only certain enantiomeric configurations are shown in the Figures, the enantiomeric orientation of the ligands may be manipulated using different reagents during synthesis. The enantiomers of the represented formulas are also within the scope of the invention.

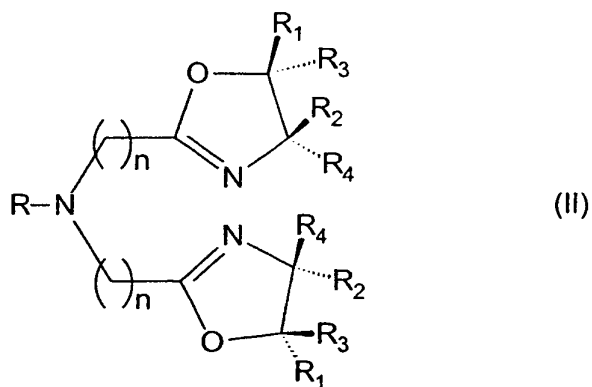
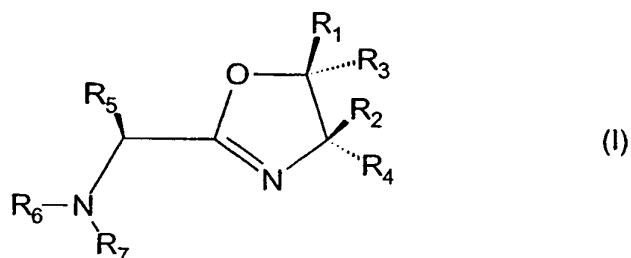
Figures (V) through (XI) of **Figure 3** denote particularly preferred embodiments of the chiral amine oxazolinyl ligands of the present invention, such as, oxazolin-2-yl-methylamine, which may be substituted on the oxazole or the methyl as shown in Formula (V), or 2-oxazolin-2-yl-azacyclopentane which may be substituted on the oxazole as shown in Formula (VI), or the previously described bis[4-(R)-phenyloxazolin-2-yl-methyl]amine, which may be derived from Formula (VII).

In summary, this invention includes new chiral tridentate ligands which form a highly efficient catalyst with $\text{RuCl}_2(\text{PPh}_3)_3$ and other catalyst precursors for transfer hydrogenation of a range of ketones and other reactions.

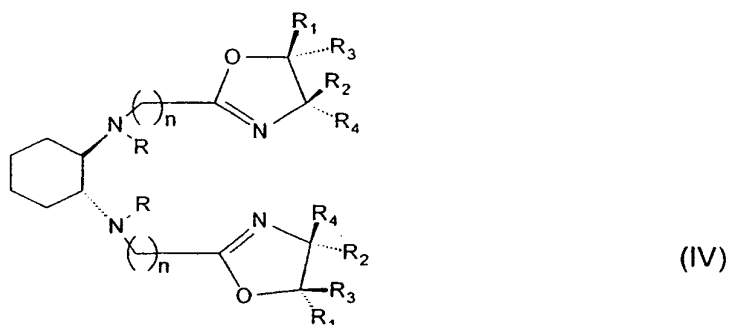
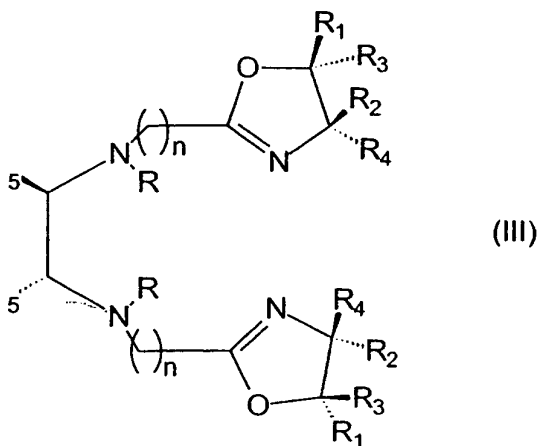
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Claims

1. A chiral ligand that forms a catalyst providing enhanced enantiomeric selectivity in asymmetric reactions, having a structure selected from the group consisting of the enantiomers of the following formulas (I) through (IV):



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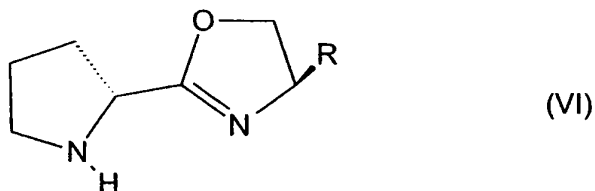
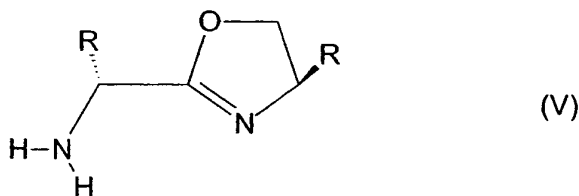


wherein R_1 , R_2 , R_3 , R_4 , R_5 , R_6 and R_7 are independently hydrogen, alkyl, aryl, substituted alkyl or substituted aryl, wherein any two of R_1 , R_2 , R_3 and R_4 may be linked to each other to form a ring structure, wherein any two of R_5 , R_6 or R_7 may be linked to each other to form a ring structure, and wherein n is 1 or 2.

2. The chiral ligand of claim 1, wherein said ligand is complexed with a transition metal.

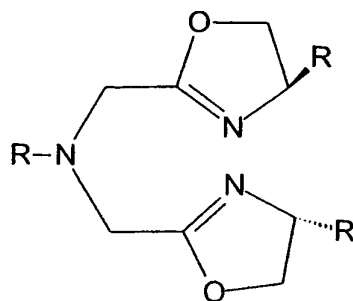
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3. The chiral ligand of claim 2, wherein said transition metal is selected from the group consisting of rhodium, iridium, ruthenium, and palladium.
4. The chiral ligand of claim 1, wherein said ligand is complexed with a transition metal catalyst precursor selected from the group consisting of $[\text{Rh}(\text{cod})\text{Cl}]_2$, $[\text{Rh}(\text{cod})_2]\text{X}$, $[\text{Ir}(\text{cod})\text{Cl}]_2$, $[\text{Ir}(\text{cod})_2]\text{X}$, $\text{Ru}(\text{cod})\text{Cl}_2$, where cod is 1,5-cyclooctadiene, and X is BF_4 , ClO_4 , SbF_6 , or CF_3SO_3 .
5. The chiral ligand of claim 1, wherein said ligand is complexed with a transition metal catalyst precursor selected from the group consisting of $\text{RuCl}_2(\text{PPh}_3)_3$, $\text{RuHCl}(\text{PPh}_3)_3$, $\text{RuX}_2(\text{PR}_3)_3$, $\text{RuHX}(\text{PR}_3)_3$, RuX_2 , wherein X is halogen and R is a substituted or unsubstituted alkyl or aryl group.
6. The chiral ligand of claim 1, wherein said ligand is selected from the group consisting of the following formulas (V) to (XI):

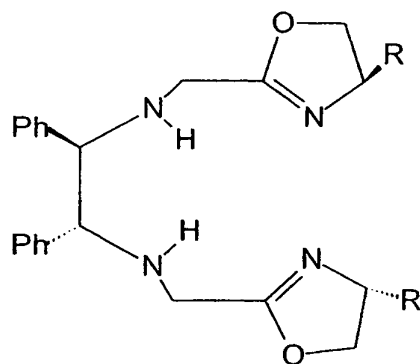


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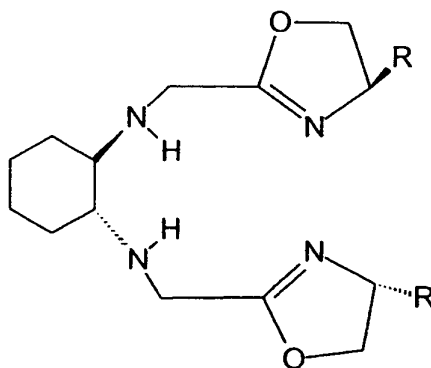
- 17 -



(VII)



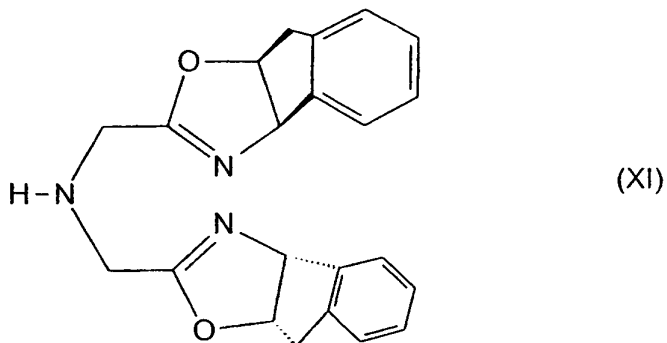
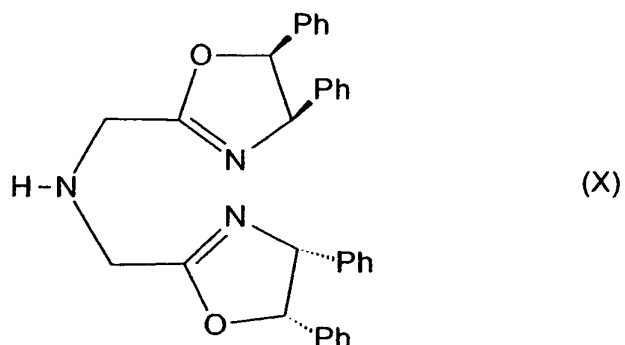
(VIII)



(IX)

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7. A chiral ligand that forms a catalyst providing enhanced enantiomeric selectivity in asymmetric reactions, said chiral ligand comprising a bis(oxazoliny) amine.

8. A chiral ligand according to claim 1, wherein said chiral ligand is bis[4-(R)-phenyloxazolin-2-yl-methyl]amine.

9. A process for making a catalyst providing enhanced enantiomeric selectivity in asymmetric reactions comprising reducing an imidate ester with a chiral alcohol to obtain the chiral ligand of claim 1.

10. A process according to claim 9 further comprising complexing said chiral ligand with a catalyst precursor comprising a transition metal.

11. A process for making a catalyst according to claim 10, wherein said catalyst precursor further comprises triphenylphosphine, and wherein said process for making the catalyst includes removing free

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triphenylphosphine released during complexation of the chiral ligand with the catalyst precursor.

12. A process for making a catalyst according to claim 10, wherein said catalyst precursor and said chiral ligand are refluxed with an alcohol at the reflux temperature of the alcohol.

13. A process for making a catalyst according to claim 10, wherein said transition metal is selected from the group consisting of rhodium, iridium, ruthenium, and palladium.

14. A process for making a catalyst according to claim 10, wherein said catalyst precursor is selected from the group consisting of $[\text{Rh}(\text{cod})\text{Cl}]_2$, $[\text{Rh}(\text{cod})_2]\text{X}$, $[\text{Ir}(\text{cod})\text{Cl}]_2$, $[\text{Ir}(\text{cod})_2]\text{X}$, where cod is 1,5-cyclooctadiene, and X is BF_4 , ClO_4 , SbF_6 , or CF_3SO_3 .

15. A process for making a catalyst according to claim 10, wherein said catalyst precursor is selected from the group consisting of $\text{RuCl}_2(\text{PPh}_3)_3$, $\text{RuHCl}(\text{PPh}_3)_3$, $\text{RuX}_2(\text{PR}_3)_3$, $\text{RuHX}(\text{PR}_3)_3$, RuX_2 , wherein X is halogen and R is a substituted or unsubstituted alkyl or aryl group.

16. A method for enhancing the enantiomeric selectivity of a chemical reaction comprising contacting a substrate with a catalyst comprising the chiral ligand of claim 1.

17. A method according to claim 16, wherein said reaction is selected from the group consisting of hydrogenation, hydride transfer reaction, hydrosilylation, hydroboration, hydrovinylation, hydroformylation, hydrocarboxylation, allylic alkylation, cyclopropanation, Diels-Alder reaction, Aldol reaction, Heck reaction, Michael addition and rearrangement.

18. A method according to claim 17, wherein said reaction is a transfer hydrogenation and said substrate is a ketone or an imine.

19. The method according to claim 18, wherein the contacting of the substrate with the catalyst further comprises contacting said substrate and said catalyst with a base and wherein the molar ratio of said base to said catalyst is between 0.5 and 2.0.

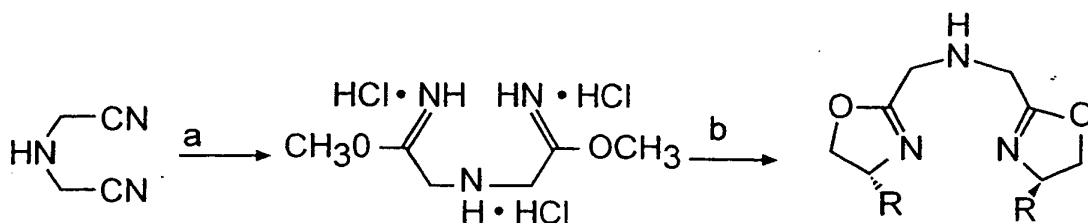
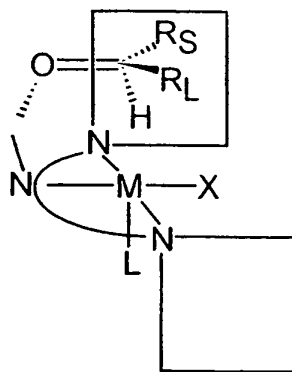
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20. The method according to claim 19, wherein said molar ratio is approximately 1.0.

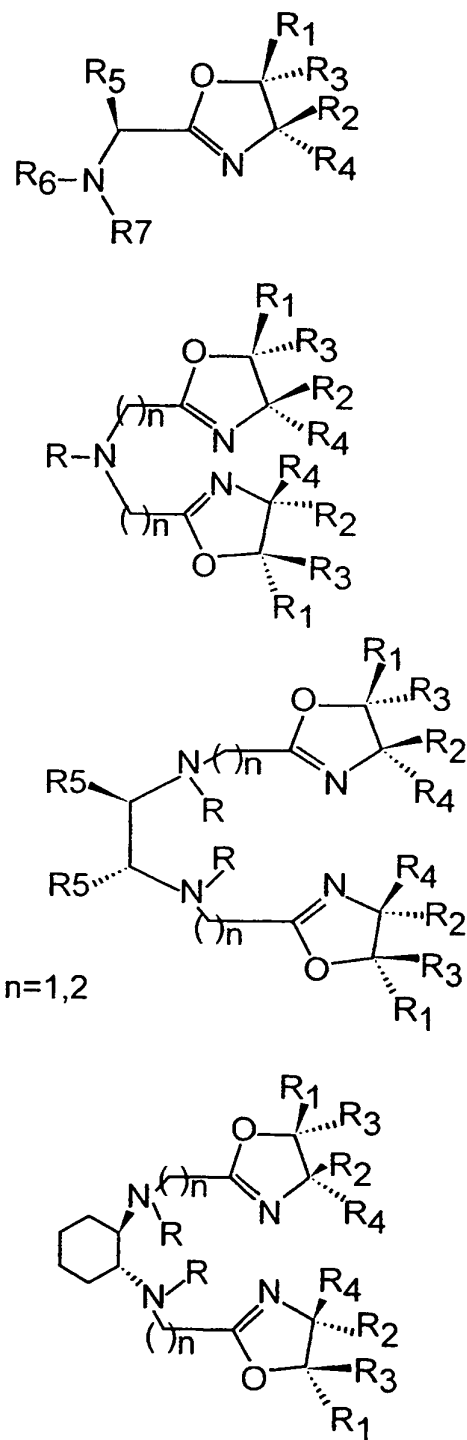
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**FIG. 1****FIG. 4**

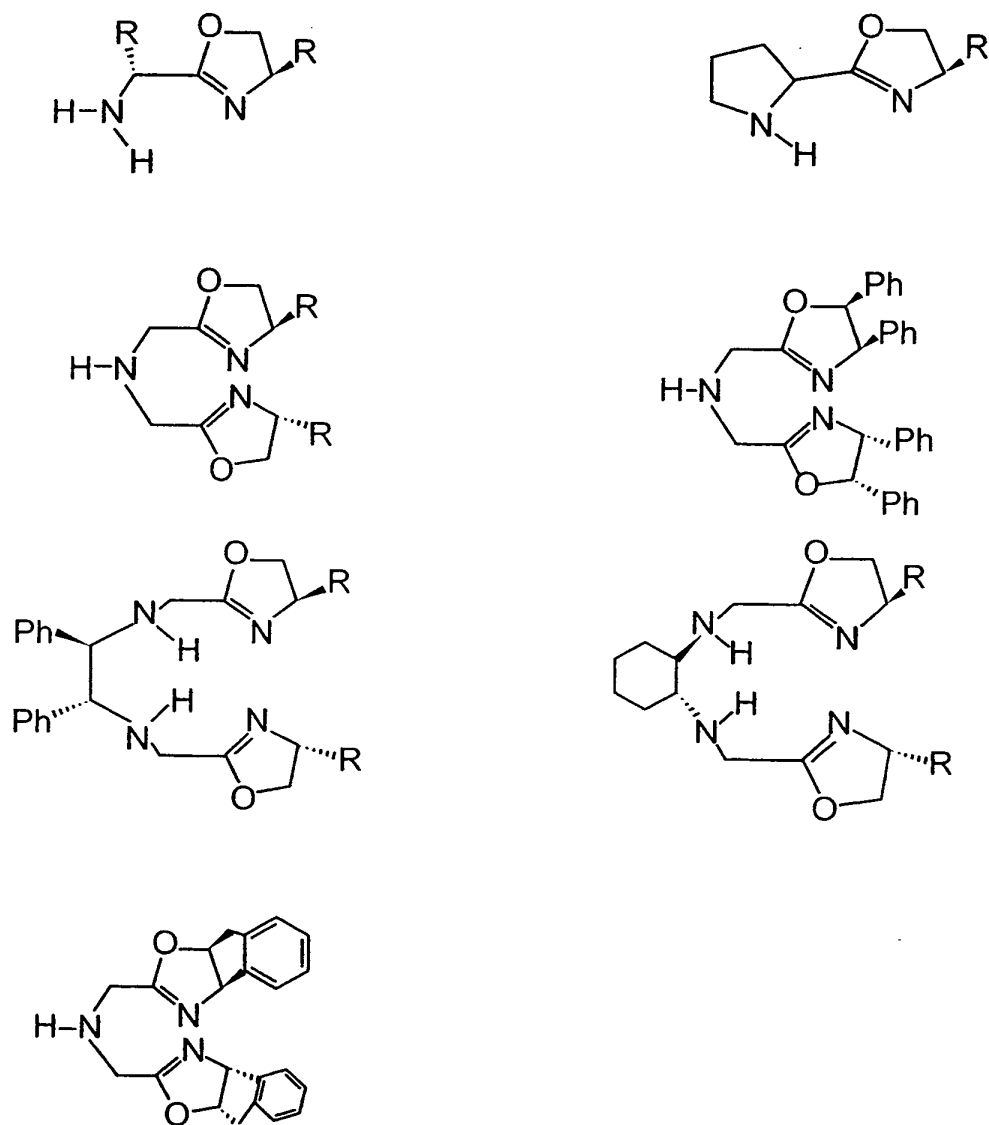
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**FIG. 2**

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**FIG. 3**

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INTERNATIONAL SEARCH REPORT

I. International Application No PCT/US 98/24036		
A. CLASSIFICATION OF SUBJECT MATTER IPC 6 C07D263/10 C07C29/143 C07B53/00 C07D263/62 B01J31/18		
According to International Patent Classification (IPC) or to both national classification and IPC		
B. FIELDS SEARCHED Minimum documentation searched (classification system followed by classification symbols) IPC 6 C07D C07C B01J C07B		
Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched		
Electronic data base consulted during the international search (name of data base and, where practical, search terms used)		
C. DOCUMENTS CONSIDERED TO BE RELEVANT		
Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	YUTONG J ET AL: "New Chiral Ligands for Catalytic Asymmetric Transfer Hydrogenation of Ketones" TETRAHEDRON LETTERS, vol. 38, no. 37, 15 September 1997, page 6565-6568 XP004089456 see the whole document	1-20
A	EP 0 780 157 A (BASF AG) 25 June 1997 see the whole document	1-20
-/--		
<div style="display: flex; justify-content: space-between;"> <input checked="" type="checkbox"/> Further documents are listed in the continuation of box C. <input checked="" type="checkbox"/> Patent family members are listed in annex. </div>		
* Special categories of cited documents : <div style="display: flex; justify-content: space-between;"> <div style="width: 45%;"> <p>"A" document defining the general state of the art which is not considered to be of particular relevance</p> <p>"E" earlier document but published on or after the international filing date</p> <p>"L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)</p> <p>"O" document referring to an oral disclosure, use, exhibition or other means</p> <p>"P" document published prior to the international filing date but later than the priority date claimed</p> </div> <div style="width: 45%;"> <p>"T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention</p> <p>"X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone</p> <p>"Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art.</p> <p>"&" document member of the same patent family</p> </div> </div>		
Date of the actual completion of the international search <div style="text-align: center; font-weight: bold;">2 March 1999</div>		Date of mailing of the international search report <div style="text-align: center; font-weight: bold;">16/03/1999</div>
Name and mailing address of the ISA European Patent Office, P.B. 5818 Patentlaan 2 NL - 2280 HV Rijswijk Tel. (+31-70) 340-2040, Tx. 31 651 epo nl, Fax: (+31-70) 340-3016		Authorized officer <div style="text-align: center; font-weight: bold;">Henry, J</div>

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INTERNATIONAL SEARCH REPORT

In tional Application No
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C.(Continuation) DOCUMENTS CONSIDERED TO BE RELEVANT

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P,X	YUTONG JIANG ET AL: "A new chiral bis(oxazolinylmethyl)amine ligand for Ru-catalysed asymmetric transfer hydrogenation of ketones" JOURNAL OF THE AMERICAN CHEMICAL SOCIETY., vol. 120, no. 15, 1998, pages 3817-3818, XP002093755 DC US see the whole document ---	1-20
P,A	GHOSH A K ET AL: "C2-Symmetric chiral bis(oxazoline)-metal complexes in catalytic asymmetric synthesis" TETRAHEDRON: ASYMMETRY, vol. 9, no. 1, 16 January 1998, page 1-45 XP004106918 see the whole document -----	1-20

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International Application No

PCT/US 98/24036

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		CA 2192226 A	23-06-1997
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